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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/609,218	06/27/2003	Vincent Ling	GNN-010CPDV	7566

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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/609,218	LING ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *4 and 8-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-7, and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1 – 15 are pending.

Applicant's election with traverse of Group I, claims 1 – 8 and 13 – 15, drawn to methods for determining the mRNA levels of one or more molecules associated with evaluation of risk and diagnosis of spontaneous abortion, in the reply filed on 08/20/2004, is acknowledged. Applicant further elects the species of VCAM.

Applicant points out that Groups III and IV should contain claims 9-12 and 13-15, instead of 1-8 and 13-15. The correction is acknowledged.

The traversal is on the ground(s) that searches necessary for Groups I and II would be co-extensive and therefore would constitute no serious burden on the examiner. This is not found persuasive because mRNA and protein do not share a disclosed common structure essential for common utility; therefore, the methods differ in their ingredients, method steps, and endpoints. In addition, they have acquired a separate status in the art as shown by different classification and recognized divergent subject matter.

The requirement is still deemed proper and is therefore made FINAL.

Upon further consideration, the prior art search has been extended to include the species of IL-10, TNFα, and IFN-γ.

Claims 4 and 8 – 12 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected Inventions and species.

3. Claims 1 – 3, 5 – 7, and 13 – 15, as they read on methods for determining the mRNA levels of one or more molecules associated with evaluation of risk and diagnosis of spontaneous abortion, with the elected species of VCAM-1, are under consideration in the instant application.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein.

Upon review of the instant application, it is noted that the sequences disclosed at least on page 12, line 20 *are not accompanied by SEQ ID Numbers*. Applicant is reminded of the sequence rules which require a submission for all sequences of more than 9 nucleotides or 3 amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules. Applicant is reminded to amend the specification accordingly.

Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) in response to this Office Action.

5. Applicant's claim for domestic priority under 35 U.S.C. 120 is acknowledged. Application USSN 09/628,129 upon which priority is claimed appears to provide adequate support under 35 U.S.C. 112 for subject matter claimed in the instant application. However, USSN 09/362,812 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for subject matter claimed in the instant application, encompassing "prognostic and diagnostic methods for determining the mRNA levels of one or more molecules associated with evaluation of risk and diagnosis of spontaneous abortion."

Consequently, the instant claims have been accorded the priority date of 07/28/2000, the filing date of USSN 09/628,129.

If Applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

The specification on page 1, lines 1 and 2 should be amended to reflect the status of the parent applications 09/628,129 and 09/362,812.

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

7. Applicant's IDS, filed 07/19/2004, is acknowledged, and has been considered.

Applicant is required to provide the dates for References B10 – B12 and C4 – C5. All references should be dated and have page numbers.

8. (A) The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP 608.01(o). Correction of the following is required:

Claims 1 and 5 include a recitation of "spontaneous abortion," whereas specification appears to provide antecedent basis only for a more narrow recitation of "immune-mediated spontaneous abortion," e.g. on page 5, first paragraph.

Applicant is requested to identify the written support for claims 1 and 5, particularly the claimed limitations of "spontaneous abortion". Alternatively, Applicant is invited to amend the specification to provide antecedent basis for the claimed subject matter.

(B) The specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, at least on page 11. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

(C) Applicant is reminded of the following and should amend the specification accordingly (page 21). The current address of the ATCC is as follows:

American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

9. Claim 1 is objected to because of the following informalities: an apparently misspelled word in the phrase "one ore more." Appropriate correction is required.

Claims 4 and 8 are objected to because of the following informalities: an apparently supernumerary parenthesis is present at the end of the sentence. Appropriate correction is required.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1 – 3, 5 – 7, and 13 - 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 1 and 5, and claims dependent thereon, are indefinite and unclear in their recitation for being incomplete by omitting essential steps or ingredients, such omission amounting to a gap between the steps. See MPEP § 2172.01.

For example, there appear insufficient steps and ingredients to carry out the prognostic or diagnostic methods of determining spontaneous abortion by detecting the presence or level of mRNA of an adhesion molecule, an inflammatory cytokine, of an immune cell surface molecule in a biological sample. For example, there appears to be insufficient correlative step (e.g. what level of a given molecule is indicative of an increased risk of spontaneous abortion?). The claims lack clear positive process steps and ingredients to carry out the claimed methods.

(B) Claims 3 and 7 are indefinite in improper recitation of a species in a Markush group. See MPEP §2174.05(h).

Base claims 1 and 5 recite "inflammatory cytokines," whereas dependent claims 3 and 7 recite "inflammatory cytokines" selected from the group consisting of, among others, IL-10. IL-10 is known in the art as an "anti-inflammatory cytokine" (see e.g. Chaouat et al., J. Immunol., 1995, vol. 154, pp. 4261-4268; of record, reference A16 on IDS filed 07/19/2004; in particular page 4261 first paragraph). Thus the metes and bounds of the phrase "inflammatory cytokines" are vague and indefinite.

(C) Claim 13 is indefinite in recitation of an "appropriate control," because the term "appropriate" is a relative term which renders the claims indefinite. The term is not defined by the claim, and the specification does not provide a sufficient standard for ascertaining which control would be appropriate. Thus one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

(D) Claim 5 is indefinite in the recitation of a "diagnostic method for determining whether a subject is suffering from spontaneous abortion," because it is unclear whether the method is directed to the moment in time when the loss of the products of conception actually occurs, to detection of the outcome of the loss, or to diagnosing the

cause of infertility. Thus the metes and bounds of the phrase "diagnostic method for ... spontaneous abortion" are vague and indefinite.

(E) Claim 13 is indefinite in that it is dependent on a non-elected claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.

(F) Claim 14 is indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of ..." with the use of the conjunction "and" rather than "or" in listing the species.

(G) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1 – 3, 5 – 7, and 13 - 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification dos not provide a sufficient enabling description of the claimed invention.

(A) The specification discloses that the mRNA levels of VCAM-1 and certain other molecules are "elevated" in placental samples of abortion-prone mice (page 54

second paragraph), and graphs in Figure 6 A – V illustrate the degree of "elevation." However, a person of skill in the art is not enabled to determine whether the difference in the mRNA levels between the abortion-prone and control samples is statistically significant or reproducible as a prognostic or diagnostic method. There is insufficient enabling disclosure of the numbers of mice sampled, the numbers of times the experiments were repeated, the deviation of values between different experiments, etc., beyond the statement that "duplicate samples" were processed (page 51 bottom paragraph).

(B) The elected claims are directed to a prognostic or diagnostic method for determining whether the subject is at risk of developing spontaneous abortion by determining the presence or level of mRNA encoding VCAM-1, IL-10, TNFα, and IFN-γ. The specification discloses that the mRNA levels of VCAM-1 and certain other molecules are "elevated" in placental samples of abortion-prone mice (page 54 second paragraph). However, a person of skill in the art is not enabled to determine what degree of "elevation" in the mRNA level would be prognostic or diagnostic for each of the claimed molecules. There is insufficient enabling disclosure of how the mRNA levels for each of the claimed molecules must differ from the control levels for the value to be considered prognostic or diagnostic of spontaneous abortion.

(C) The specification discloses on page 54 (Example 11) and Figure 6 A – V the results of comparison of mRNA levels of a number of molecules in placental samples obtained from abortion prone mice and normal (control) mice. In particular, mRNA levels for certain cell adhesion molecules, such as VCAM-1, are apparently elevated in abortion-prone mice, while other cell adhesion molecules, such as ICAM and PECAM, are not affected (page 54 and Figures 6B and 6C). Therefore, the disclosure is not enabling for a broadly defined genus of "adhesion molecules." Likewise, although examples of specific inflammatory cytokines are disclosed on page 54, the disclosure is not enabling for a broadly defined genus of "inflammatory cytokines."

(D) The specification discloses on page 54 (Example 11) and Figure 6 A – V the results of comparison of mRNA levels of a number of molecules in placental samples obtained from abortion prone mice and normal (control) mice. The specification does not provide sufficient objective evidence that supports the predictive or diagnostic nature of the claimed methods when applied to "biological samples" of tissues other than the placenta, or whether mere detection of the presence or level of mRNA, without comparing it to the level in a control sample, would be prognostic or diagnostic for spontaneous abortion. Furthermore, Daniel et al. (Am. J. Reprod. Immunol., 2000, V. 43, pp. 92 – 97), disclose that the soluble form of VCAM-1 in the serum "is not appropriate to serve as a marker for pregnancy viability," i.e. is not predictive or diagnostic of the risk of spontaneous abortion.

(E) Claim 5 includes a recitation of a "diagnostic method for determining whether a subject is suffering from spontaneous abortion." The specification does not provide a sufficient enabling disclosure of the claimed method, e.g. at what point in time relative to the loss of the products of conception the sample should be obtained to be of diagnostic value. If the sample is to be obtained at the moment the subject is suffering from abortion, the event first has to be diagnosed by other means, which are not disclosed, and which make the claimed methods redundant. Without sufficient enabling disclosure on how the sample collection relates to the process of spontaneous abortion, a person of skill in the art is not enabled practice the claimed methods.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective prognostic or diagnostic evaluation of risk of spontaneous abortion, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for prognostic or diagnostic evaluation of risk of spontaneous abortion.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1, 3, 5, 7, and 13 – 15 are rejected under **35 U.S.C. 102(b)** as being anticipated by Chaouat et al. (J. Immunol., 1995, vol. 154, pp. 4261-4268; of record, reference A16 on IDS filed 07/19/2004; see entire document).

Chaouat et al. teach that placentae of fetal resorption-prone mice, i.e. those at increased risk and high incidence of spontaneous abortion, produce increased levels of inflammatory cytokines TNFα and IFN-γ, and reduced levels of anti-inflammatory cytokines IL-4 and IL-10, compared to a reproductively normal strain of mice (see entire document, in particular, first paragraph of Results on page 4263, and Figure 1). Chaouat et al. further review that the levels of both mRNA and protein of inflammatory cytokines are locally elevated when compared to reproductively normal pregnancies (page 4263 paragraph 1 of Results, and page 4266 left column bottom paragraph). Chaouat et al. further teach that there is a "tight linkage between fetal rescue and the induction of an anti-inflammatory environment in the placenta," i.e. the inflammatory environment is prognostic or diagnostic of spontaneous abortion. Inherent in these teachings is the prognostic or diagnostic value of levels of inflammatory cytokines in the placenta.

Preamble language in claims of patents directed to prognosing or diagnosing a disease are expressions of purposes and intended results, and as such are non-limiting, since language does not result in manipulative differences in steps of claims. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC

2001). Although the reference is silent about methods of prognosing or diagnosing spontaneous abortion, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure.

The reference teachings thus anticipate the claimed invention.

16. The following is a quotation of **35 U.S.C. 103(a)** which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1, 3, 5, 7, and 13 – 15 are rejected under **35 U.S.C. 103(a)** as being unpatentable over Chaouat et al. (1995; of record, reference A16 on IDS filed 07/19/2004; see entire document) and further in view of Busfield (US Pat. No. 6,194,151; see entire document).

The claims are drawn to a prognostic or diagnostic method for determining a risk for spontaneous abortion by detecting the level of mRNA of one or more of an adhesion

molecule, an inflammatory cytokine, or an immune cell surface molecule in a sample obtained from a subject.

Chaouat et al. have been discussed supra, and teach that placentae of fetal resorption-prone mice (those characterized by increased risk and high incidence of spontaneous abortion) produce increased levels of inflammatory cytokines TNFα and IFN-γ, and reduced levels of anti-inflammatory cytokines IL-4 and IL-10, compared to a reproductively normal strain of mice (see entire document, in particular, first paragraph of Results on page 4263, and Figure 1). Chaouat et al. further teach that there is a "tight linkage between fetal rescue and the induction of an anti-inflammatory environment in the placenta," i.e. the levels of inflammatory cytokines in the placenta are prognostic or diagnostic of spontaneous abortion.

The reference differs from the instant claims in that Chaouat et al. do not exemplify determination of the mRNA levels of the corresponding cytokines. However, it was well known and practiced at the time the invention was made to evaluate the expression of a protein by detecting the level of the corresponding mRNA. For example, Busfield teaches that nucleic acids and antibodies can be used in diagnostic and prognostic assays to detect protein and mRNA in biological samples, e.g. in inflammatory diseases (see entire document, in particular, Uses and Methods of the Invention, columns 38 – 39).

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the risk of spontaneous abortion by detecting the levels of inflammatory cytokines in placental samples, as taught by Chaouat et al., by measuring the levels of the corresponding mRNA, as taught by Busfield. One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because, as reviewed by Chaouat et al., enhanced fetal death appears to correlate with, or even be mediated by, local NK activity and infiltration, perhaps through

the stimulation of secretion of inflammatory cytokines (see page 2266, left column bottom paragraph). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success, because, as taught by Busfield, both protein and mRNA levels can be used in diagnostic and prognostic assays.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. Conclusion: no claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI
Patent Examiner
Art Unit 1644
October 19, 2004

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10/28/04